REMARKS

Claims 1 to 15, 34 and 35 are pending in the present application. Claims 11 and 12 have been indicated to be allowable. Claims 2, 3, 7, 13, 14 and 35 have been amended herein and claims 1, 15 and 34 have been cancelled herein without prejudice to Applicants' pursuing these claims in a related application that claims the benefit of priority to the subject application. New claims 36 to 42 have been added herein. Therefore, upon entry of the amendment, claims 2 to 14 and 35 to 42 will be under examination.

Regarding the amendments

Claims 2 and 3 have been amended to recite a "PrRP receptor signal" in place of a "predetermined signal." These amendments are supported in the specification, for example, at page 31, line 27, to page 32, line 1, which states that a predetermined signal is an indication of activation of G-protein-dependent-signal transduction through PrRP receptor.

Claims 2, 7 and 35 have been amended to independent form. These amendments are supported, for example, by claim 1 and 2; 1 and 7; and 15 as originally filed, respectively.

New claim 36 depends from claim 35, and recites a PrRP that is a polypeptide containing SEQ ID NO:23. New claim 36 is

supported in the specification, for example, at page 24, lines 5-7.

New claim 37 depends from claim 36, and recites a PrRP that is a polypeptide containing an amino acid sequence selected from SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17 and SEQ ID NO:18. New claim 37 is supported in the specification, for example, at page 19, lines 20-24; and page 20, lines 1-6.

New claim 38 depends from claims 37, and recites a PrRP that is a polypeptide containing an amino acid sequence selected from SEQ ID NO:13, SEQ ID NO:14 and SEQ ID NO:15. New claim 38 is supported in the specification, for example, at page 19, lines 20-24.

New claims 39 and 40 depend from claim 7; new claims 41 and 42 depend from claim 11. These new claims are parallel to claims 13 and 14 as originally filed. New claims 39 to 42 are supported, for example, by claims 7 and 11 as originally filed, respectively, and by 1, 13 and 14 as originally filed.

Regarding the rejection under 35 U.S.C. § 112, first paragraph, enablement

The objection to the specification and corresponding rejection of claims 1, 2, 15 and 34 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement in the specification, are respectfully traversed.

Regarding claims 15 and 34, the Office Action acknowledges that the specification is enabling for a method of promoting wakefulness in a mammal that involves administering to the mammal an effective amount of PrRP, but alleges that the specification lacks enablement for the claimed method when practiced using other PrRP receptor agonists. Applicants maintain that the specification provides enablement for the use of a variety of PrRP receptor agonists in the claimed methods for promoting wakefulness in a mammal. In this regard, the specification exemplifies a variety of PrRP receptor agonists (see, for example, page 19, lines 20-2; page 20, lines 1-6; and page 24, lines 5-7), and provides extensive guidance that would have allowed one skilled in the art use PrRP receptor agonists having diverse structural characteristics in the methods of the invention without undue experimentation (see, for example, page 29, line 21, to page 30, line 17; page 35, line 29, to page 30, line 11; and page 37, lines 9-22). Nevertheless, this rejection has been rendered moot by the cancellation of claims 13 and 34 herein. Applicants point out that claim 35 is directed to a method of promoting wakefulness in a mammal that involves administering an effective amount of a PrRP.

Regarding claim 1, the Office Action acknowledges that the specification is enabling for a method of screening for a compound for promoting wakefulness in a mammal, wherein PrRP promotes calcium ion mobilization and arachadonic acid metabolite release, but alleges that the specification lacks enablement for the claimed method when practiced using other predetermined signals. In this regard, the Office Action alleges that "any signal can be a predetermined signal."

Moreover, Applicants submit that the specification teaches that a predetermined signal useful in a method of the invention is a readout that is an indication of activation of G-protein-dependent signal transduction through PrRP receptor (page 31, line 27, to page 32, line 1). In view of this teaching in the specification, Applicants submit that those skilled in the art would have understood that a variety of signals resulting from activation of PrRP would be useful in the claimed methods. To emphasize that the predetermined signal is not "any signal," but instead is a readout of activation of G-protein-dependent signal transduction through PrRP receptor, Applicants have replaced the term "predetermined signal" with "PrRP receptor signal."

The specification teaches that a signal other than arachadonic acid metabolite release or Ca^{2+} influx can be used as the readout in the methods of the invention, if desired (page 32, lines 24-26). Such other readouts for PrRP receptor activation described in the specification include increased or

decreased production or liberation of second messengers such as acetylcholine, diacylglycerol, cGMP, cAMP, inositol phosphate and ions; altered cell membrane potential; GTP hydrolysis, influx or efflux of amino acids; increased or decreased phosphorylation of intracellular proteins, and activation of transcription (page 33, lines 14-21). The specification further teaches that any convenient G-protein mediated signal transduction pathway can be assayed, for example, using a chimeric G containing a C-terminal residues of a G_{α} that couples to PrRP receptor, such as $G_{\alpha q}$ (page 33 lines 2-8).

The specification provides additional guidance for assaying predetermined signals in addition to calcium ion mobilization and arachadonic acid metabolite release, for example, by citing protocols for screening assays using voltage changes and gene expression (page 34, lines 1-6), as well as yeast bioassays (page 34, lines 6-9). Applicants submit that undue experimentation would not have been required for one skilled in the art to use any of variety of assays for determining activation of G-protein-dependent signal transduction through PrRP receptor, because G-protein coupled receptor signaling and binding screening assays, such as those described and referenced in the specification, were routine at the time of filing the subject application.

In view of the above remarks, Applicants respectfully request that the Examiner reconsider and remove the enablement rejection under the first paragraph of 35 U.S.C. §112.

Regarding the rejection under 35 U.S.C. § 112, first paragraph, written description

The objection to the specification and corresponding rejection of claims 1, 15 and 34 under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient description of the claimed method to reasonably convey to one skilled in the relevant art that the inventors were in possession of the claimed invention at the time the application was filed, are respectfully traversed.

The Office Action acknowledges that the specification provides adequate written description for a method of promoting wakefulness in a mammal that involves administering to the mammal an effective amount of PrRP comprising SEQ ID NO:23, but alleges that there is insufficient descriptive support for the genus "PrRP receptor agonists" or "PrRP functional analogs."

Applicants maintain that the specification provides written description sufficient to convey to one skilled in the art that Applicants had possession of the invention of claims 1, 15 and 34. Regarding claims 15 and 34, given the guidance disclosed in the specification regarding structural attributes of multiple exemplary PrRP receptor agonists and functional analogs (see for example, page 19, lines 20-24; page 20, lines 1-6; and page 23, line 28, to page 24, line 5) as well as functional attributes of a PrRP receptor agonist (see, for example, page 18, lines 11-13), it would have been clear to the skilled artisan that Applicants were in possession of the

claimed method of promoting wakefulness in an animal at the time the application was filed. Nevertheless, claim 15 has been amended to recite a PrRP. This rejection has been rendered moot with respect to claims 1 and 34, which have been cancelled herein.

In view of the above remarks and amendments, Applicants respectfully request that the Examiner reconsider and remove the written description rejection under the first paragraph of 35 U.S.C. § 112.

Regarding the indefiniteness rejection

The rejection of claim 2 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed. Applicants submit that claim 2 is clear and definite as written.

Claim 2 stands rejected as indefinite for reciting the term "predetermined." Applicants submit that the meaning of the term "predetermined signal" would have been clear to one skilled in the art based on teachings in the specification. The specification states, for example, that a "predetermined signal" refers to a readout, detectable by any analytical means, that is a qualitative or quantitative indication of activation of G-protein-dependent signal transduction through PrRP receptor (page 31, line 27, to page 32, line 1). In view of this teaching, Applicants submit that claim 2 is clear and definite as originally written. Nevertheless, claim 2 has been amended to remove the objected term. Accordingly, Applicants request

removal of this rejection under 35 U.S.C. § 112, second paragraph.

Regarding the rejections under 35 U.S.C. § 102(a)

The rejection of claims 1, 15, 34 and 35 under 35 U.S.C. § 102(a), as allegedly anticipated by Zhang et al. Society for Neuroscience Abstracts (1999) is respectfully traversed. The Office Action asserts that the cited reference indicates that high doses of PrRP did not effect REM sleep, but enhanced nonREM sleep. Based on this assertion, the Office Action concludes that Zhang et al. describes PrRP induced promotion of wakefulness because "one skilled in the art could interpret those results to mean that the rats are coming out of a deep sleep (REM sleep) into a lighter sleep (nonREM sleep); i.e. promoting wakefulness." Applicants disagree with this interpretation of data presented in Zhang et al.

Applicants submit that Zhang et al. states that nonREM sleep was enhanced by 27.2% by administration of 10 nmol PrRP, but indicates no reduction in REM sleep after 10 nmol PrRP, or any other dose tested. Without any indication that either nonREM or REM sleep was reduced by PrRP treatment, the assertion that treated rats "are coming out of REM sleep" is invalid. Specifically, Zhang et al. does not indicate that REM sleep was reduced in favor of nonREM sleep, but instead indicates only that nonREM sleep was increased—that is, the 27.2% enhancement in nonREM sleep does not mean a 27.2% reduction in REM sleep. Thus, Zhang et al. describes only increases in sleep, whether

nonREM or REM sleep, and increasing sleep is the opposite of promoting wakefulness. For these reasons Applicants submit that Zhang et al. does not describe reduced sleep (REM or nonREM) in response to PrRP administration and therefore cannot describe "coming out of a deep sleep into a lighter sleep" or promoting wakefulness.

Moreover, Applicants respectfully submit that those skilled in the art would recognize that "coming out of a deep sleep (REM sleep) into a lighter sleep (nonREM sleep)" is not equivalent to "promoting wakefulness." In particular, REM sleep and nonREM sleep are complex phenomena that cannot reasonably be simplified by the terms "deep sleep" and "lighter sleep." As a basic overview of the stages of sleep, Applicants submit herewith Exhibit A, an article entitled "Sleep Stages" (online publication by Health Communities.com), which provides a lay description of sleep stages. As is described in the article, nonREM sleep stages 3 and 4 are deep sleep stages (see paragraph 6). In contrast, REM sleep as monitored by polysonography is more similar to a light sleep stage (stage 1 of nonREM) than to deep nonREM sleep (see paragraph 8). Therefore, even if Zhang et al. did describe decreased REM sleep in favor of increased nonREM sleep, such an alternation in sleep would not necessarily be equivalent to increased wakefulness.

In view of the above, Applicants submit that Zhang et al., in describing PrRP-induced increases in either or both REM and nonREM sleep, does not teach or suggest that PrRP can be used to promote wakefulness by reducing sleep. For this reason,

Applicants respectfully request removal of the rejection under 35 U.S.C. §102(a).

Regarding the rejection under 35 U.S.C. § 103

The rejections of claims 1, 13 and 14 under 35 U.S.C. § 103(a), as allegedly obvious over Zhang et al. in view of Curran et al. (U.S. Patent No. 6,323,177); and the rejection of claims 2 to 10 under 35 U.S.C. § 103(a), as allegedly obvious over Zhang et al. in view of Curran et al. and further in view of Roland et al. Endocrinology 140:5736-5745 (1999), are respectfully traversed.

Applicants submit that the combination of Zhang et al. and Curran et al. does not teach or suggest the methods of claims 1, 13 and 14, but rather teaches away from the claimed invention. Specifically, whereas claim 1 is directed to identifying a PrRP receptor agonist for promoting wakefulness in a mammal, Zhang et al. describes experimental results indicating that PrRP promotes REM sleep at a 0.1 nmol dose; promotes both REM and nonREM sleep at a 1 nmol dose; and promotes nonREM sleep at a 10 nmol dose (see, for example, the 6th and 7th sentences), indicating that PrRP does not reduce either REM or nonREM sleep at any administered dose. Curran et al. does not cure the deficiencies of Zhang et al. in describing the claimed invention. Rather, this reference describes unrelated screening and therapeutic methods (column 1, lines 12-18).

Further, Applicants maintain that the combination of Zhang et al. with Curran et al. provides no motivation for producing the claimed invention. In this regard, Zhang et al. states that administration of PrRP results in increased REM sleep, nonREM sleep or both REM and nonREM sleep (see, for example, the 6th and 7th sentences), with no reduction in either REM or nonREM sleep. Based on these results, one skilled in the art would have had no motivation to screen PrRP receptor agonists to identify a compound for promoting wakefulness, but instead would have understood that a PrRP receptor agonist promotes sleep.

Regarding the rejection of claims 2 to 10, Applicants maintain that the combination of Zhang et al., Curran et al. and Roland et al. does not teach or suggest the claimed methods. Whereas Zhang et al. indicates that administration of PrRP to rats resulted in increased sleep, the methods of claims 2 to 10 are directed to screening for a PrRP receptor agonist that promotes wakefulness. Neither Curran et al. alone or together with Roland et al. can cure the deficiencies in Zhang et al. in describing or suggesting the claimed invention.

In view of the above, Applicants submit that none of Zhang et al.; the combination of Zhang et al. with Curran et al.; or the combination of Zhang et al., Curran et al., and Roland et al., suggest or provide a motivation for producing the claimed invention. Therefore, Applicants respectively request that this ground of rejection be withdrawn.

CONCLUSION

In view of the amendments and remarks submitted herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to contact the undersigned agent or Cathryn Campbell if there are any questions relating to this application.

Respectfully submitted,

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Sleep Stages

Since the early 20th century, human sleep has been described as a succession of five recurring stages: four non-REM stages and the REM stage. A sixth stage, waking, is often included. Waking, in this context, is actually the phase during which a person falls asleep. Rapid eye movement (REM) sleep is marked by extensive physiological changes, such as accelerated respiration, increased brain activity, eye movement, and muscle relaxation. People dream during REM sleep, perhaps as a result of excited brain activity and the paralysis of major voluntary muscles.

Sleep quality changes with transition from one sleep stage into another. Although the signals for transition between the five (or six) stages of sleep are mysterious, it is important to remember that these stages are, in fact, discretely independent of one another, each marked by subtle changes in bodily function and each part of a predictable cycle whose intervals are observable. Sleep stages are monitored and examined clinically with polysomnography, which provides data regarding electrical and muscular states during sleep.

Waking
The waking stage is referred to as relaxed wakefulness, because this is the stage in which the body prepares for sleep. All people fall asleep with tense muscles, their eyes moving erratically. Then, normally, as a person becomes sleepier, the body begins to slow down. Muscles begin to relax, and eye movement slows to a roll.

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Stage 1
Stage 1 sleep, or drowsiness, is often described as first in the sequence, especially in models where waking is not included. Polysomnography shows a 50% reduction in activity between wakefulness and stage 1 sleep. The eyes are closed during Stage 1 sleep, but if aroused from it, a person may feel as if he or she has not slept. Stage 1 may last for five to 10 minutes.

Stage 2
Stage 2 is a period of light sleep during which polysomnographic readings show intermittent peaks and valleys, or positive and negative waves. These waves indicate spontaneous periods of muscle tone mixed with periods of muscle relaxation. Muscle tone of this kind can be seen in other stages of sleep as a reaction to auditory stimuli. The heart rate slows, and body temperature decreases. At this point, the body prepares to enter deep sleep.

Stages 3 and 4
These are deep sleep stages, with Stage 4 being more intense than Stage 3. These stages are known as slow-wave, or delta, sleep. During slow-wave sleep, especially during Stage 4, the

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electromyogram records slow waves of high amplitude, indicating a pattern of deep sleep and rhythmic continuity.

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Non-REM Sleep
The period of non-REM sleep (NREM)is comprised of Stages 1-4 and lasts from 90 to 120 minutes, each stage lasting anywhere from 5 to 15 minutes. Surprisingly, however, Stages 2 and 3 repeat backwards before REM sleep is attained. So, a normal sleep cycle has this pattern: waking, stage 1, 2, 3, 4, 3, 2, REM. Usually, REM sleep occurs 90 minutes after sleep onset.

Stage 5, REM
REM sleep is distinguishable from NREM sleep by changes in physiological states, including its characteristic rapid eye movements. However, polysomnograms show wave patterns in REM to be similar to Stage 1 sleep. In normal sleep (in people without disorders of sleep-wake patterns or REM behavior disorder), heart rate and respiration speed up and become erratic, while the face, fingers, and legs may twitch. Intense dreaming occurs during REM sleep as a result of heightened cerebral activity, but paralysis occurs simultaneously in the major voluntary muscle groups, including the submental muscles (muscles of the chin and neck). Because REM is a mixture of encephalic (brain) states of excitement and muscular immobility, it is sometimes called paradoxical sleep. It is generally thought that REM-associated muscle paralysis is meant to keep the body from acting out the dreams that occur during this intensely cerebral stage. The first period of REM typically lasts 10 minutes, with each recurring REM stage lengthening, and the final one lasting an hour.

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Sleep Cycle
The five stages of sleep, including their repetition, occur cyclically. The first cycle, which ends after the completion of the first REM stage, usually lasts for 100 minutes. Each subsequent cycle lasts longer, as its respective REM stage extends. So a person may complete five cycles in a typical night's sleep.

Factors that Affect Sleep Stage and the Sleep Cycle
The sleep cycle is variable, influenced by several agents. Sleep cycles subsequent to the first one in a night's sleep typically feature less slow-wave sleep, as Stages 3 and 4 shorten. Slow-wave, deep sleep is longest early in a night's sleep. Generally, sleep disorders affect the quality, duration, and onset of sleep. Sleep deprivation, frequently changing sleep schedule, stress, and environment all affect the progression of the sleep cycle. Rapid eye movement latency (the time it takes a person to achieve REM sleep) may be affected by a sleep disorder like narcolepsy. Psychological conditions like depression shorten the duration of rapid eye movement. Also, treatment for psychiatric conditions often positively affects sleep, typically inducing some desired change in sleep habit. For example, antidepressants like Prozac® usually quicken sleep onset and lengthen REM stages. People who take antidepressants often benefit from the effects they have on the quality and duration of the sleep cycle.

Age
The percentage of REM sleep is highest during infancy and early childhood, drops off during adolescence and young adulthood, and decreases further in older age. Of course, infants require the greatest amount of sleep. As parents know, total sleep time typically

becomes shorter during childhood and may become longer again in adolescence. The stage-respective dimensions of sleep change relative to age. Stages 3 and 4 in the first sleep cycle shorten even more dramatically in older people than they do during a typical night for everyone else, so older people get less total deep sleep than younger people do. Also with age comes the lengthening of the first REM stage. Older people commonly enter REM sleep quicker and stay there longer.

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